7/21/01 JBray
#14 (NE)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 053466/0234

In re patent application of

Masayuki TSUCHIYA, *et al.*

Serial No.: **09/114,285** Group Art Unit: **1642**

Filing Date: **July 13, 1998** Examiner: **G. Bansal**

For: **RESHAPED HUMAN ANTIBODY TO HUMAN INTERLEUKIN-6 RECEPTOR**

AMENDMENT AND REPLY UNDER 37 C.F.R. §1.116

Commissioner for Patents
BOX AF
Washington, D.C. 20231

Sir:

In reply to the final Office Action dated July 26, 2000, Applicants submit the following Amendment and Reply under 37 C.F.R. § 1.116:

Don or Gabe Bansal 8/6/01

IN THE CLAIMS

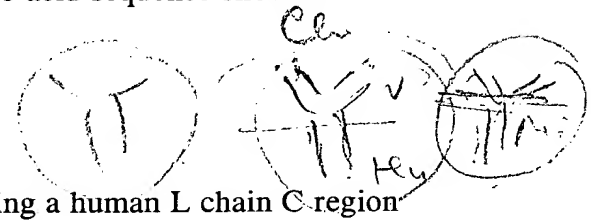
In accordance with 37 C.F.R. § 1.121, please substitute for claims 67, 71-74, 75 and 76 the following rewritten version of the same claims, as amended. The changes are shown explicitly in the attached "Version with Markings to Show Changes Made".

67. A chimeric antibody to human interleukin-6 receptor (IL-6R), comprising:

(1) light chains (L chains) each comprising a human L chain constant region (C region) and an L chain variable region (V region) of a mouse monoclonal antibody to human IL-6R; and

(2) heavy chains (H chains) each comprising a human H chain C region, and H chain V region of a mouse monoclonal antibody to human IL-6R;

wherein the mouse L chain V region includes an amino acid sequence shown in SEQ ID NO: 28 and the mouse H chain V region includes an amino acid sequence shown in SEQ ID NO: 30.



71. An isolated DNA encoding an L chain comprising a human L chain C region and an L chain V region of a mouse monoclonal antibody to human IL-6R wherein the human L chain C region is a human Kc region and the L chain V region includes the amino acid sequence set forth in SEQ ID NO: 28.

72. An isolated DNA encoding an H chain comprising a human H chain C region and an H chain V region of a mouse monoclonal antibody to IL-6R, wherein the human H chain C region is a human γ-1C region and the H chain V region includes the amino acid sequence set forth in SEQ ID NO: 30.

73. An expression vector comprising a DNA coding for an L chain comprising a human L chain C region and L chain V region of a mouse monoclonal antibody to human IL-6R, wherein the human L chain C region is a human Kc region, and the L chain V region includes an amino acid sequence shown in SEQ ID NO: 28.

74. An expression vector comprising a DNA coding for an H chain comprising a human H chain C region and H chain V region of a mouse monoclonal antibody to human

IL-6R, wherein the human L chain C region is a human Kc region, and the L chain V region includes an amino acid sequence shown in SEQ ID NO: 30.

75. A host cell co-transformed with:

(1) an expression vector comprising a DNA coding for an L chain comprising a human L chain C region and an L chain V region of a mouse monoclonal antibody to human IL-6R, and with

(2) an expression vector comprising a DNA coding for an H chain comprising a human H chain C region and an H chain V region of a mouse monoclonal antibody to IL-6R, wherein the human L chain C region is a human Kc region; the L chain V region includes an amino acid sequence shown in SEQ ID NO: 28, the human L chain C region is a human γ-1C region and the H chain V region includes an amino acid sequence shown in SEQ ID NO: 30.

76. A method of producing the chimeric antibody to human IL-6R according to claim 67, said method at least comprising the steps of:

(a) culturing host cells co-transformed with a first expression vector and a second expression vector, for a time and under conditions sufficient for expression to occur, wherein the first expression vector comprises DNA encoding a human L chain C region and a mouse L chain V region including the sequence set forth in SEQ ID NO: 28 and the second expression vector comprises DNA encoding a human H chain C region and a mouse H chain V region including a sequence set forth SEQ ID NO: 30; and

(b) recovering the chimeric antibody from the culture.

REMARKS

Status of the Claims

By this amendment, claims 67 and 71-76 are amended. Accordingly, upon entry of this Amendment, claims 67-76 will remain pending in the application.

Claims 67 and 71-76 are amended to place the present application into better condition for allowance. The amendments to the claims remove an embodiment of the present invention and do not add new matter in any way.

Rejection Under 35 U.S.C. § 103 (a)

Claims 69-76 are rejected by the Examiner under 35 U.S.C. § 103 (a) as being unpatentable over Hirata or Kishimoto in view of Oi or Morrison. Applicants respectfully request reconsideration and withdrawal of the rejection.

Present Invention

The present invention, as amended, relates to a chimeric antibody to human interleukin-6 receptor, comprising: (1) light chains, each comprising a human light chain constant region and a light chain variable region of a mouse monoclonal antibody to human IL-6R and (2) heavy chains, each comprising a human heavy chain constant region, and a heavy chain variable region of a mouse monoclonal antibody to human IL-6R; wherein the mouse light chain variable region includes an amino acid sequence shown in SEQ ID NO: 28 and the mouse heavy chain variable region includes an amino acid sequence shown in SEQ ID NO: 30.

Distinctions Over the Cited Art.

The present invention, as amended, is not obvious over Hirata or Kishimoto in view of Oi or Morrison because the cited references fail to teach the unexpected result that the chimeric PM-1 antibody of the present invention has superior properties of inhibition of multiple myeloma cell growth. These superior properties are illustrated in the attached Exhibits 1 and 2, K. Sato et al., Cancer Research, Vol. 53, p. 851-856, 1993 and K. Sato et al., Molecular Immunology, Vol. 31, No. 5, p. 371-381, 1994, respectively.

Superior inhibition of multiple myeloma cell growth by chimeric PM-1 antibody as compared to PM-1 antibody is illustrated by the data reported in Figure 5 (p. 854) of Exhibit 1. The Examiner notes that the text to Figure 5 of Exhibit 1 states that the effect of the PM-1 antibodies on multiple cell growth is equivalent. The data, however, shows that the effect of the chimeric PM-1 antibody is greater than that of the PM-1 antibody. It is important to note that the antibody concentration on the X axis is represented by a logarithmic scale, therefore, antibody concentrations that appear equivalent are truly different. Therefore, the data reported in Figures 5A-C illustrates that the effect of chimeric PM-1 antibody is greater than that of the PM-1 antibody.

Superior inhibition of multiple myeloma cell growth by chimeric PM-1 antibody as compared to PM-1 antibody is illustrated in Figure 5A of Exhibit 1. Figure 5A of Exhibit 1 shows a comparison of the effect of PM-1 antibody and chimeric PM-1 antibody on multiple myeloma cell growth using MMS1 cells. In Figure 5A of Exhibit 1, the hollow triangles represent PM-1 antibody and the hollow circles represent chimeric PM-1 antibody. A rough estimation of IC_{50}'s for the PM-1 antibody and the chimeric PM-1 antibody are 1700 ng/ml and 610 ng/ml, respectively. Thus, it appears that the inhibitory

activity of the chimeric PM-1 antibody is more than 2.5 times higher than that of the PM-1 antibody. A person of ordinary skill in the art would not have expected this superior activity for the chimeric PM-1 antibody.

Superior inhibition of multiple myeloma cell growth by chimeric PM-1 antibody as compared to PM-1 antibody is also illustrated by the data reported in Figure 5B (p. 854) of Exhibit 1. Figure 5B of Exhibit 1 shows a comparison of the effect of PM-1 antibody and chimeric PM-1 antibody on multiple myeloma cell growth using ILKM3 cells. In Figure 5B of Exhibit 1, the hollow triangles represent PM-1 antibody and the hollow circles represent chimeric PM-1 antibody. A rough estimation of IC_{50}'s for the PM-1 antibody and the chimeric PM-1 antibody are 1000 ng/ml and 300 ng/ml, respectively. Thus, it appears that the inhibitory activity of the chimeric PM-1 antibody is more than 3 times higher than that of the PM-1 antibody. A person of ordinary skill in the art would not have expected this superior activity for the chimeric PM-1 antibody.

Additionally, superior inhibition of multiple myeloma cell growth by chimeric PM-1 antibody as compared to PM-1 antibody is illustrated by the data reported in Figure 5C (p. 854) of Exhibit 1. Figure 5C of Exhibit 1 shows a comparison of the effect of PM-1 antibody and chimeric PM-1 antibody on multiple myeloma cell growth using S6B45 cells. In Figure 5C of Exhibit 1, the hollow triangles represent PM-1 antibody and the hollow circles represent chimeric PM-1 antibody. A rough estimation of IC_{50}'s for the PM-1 antibody and the chimeric PM-1 antibody are 310 ng/ml and 190 ng/ml, respectively. Thus, it appears that the inhibitory activity of the chimeric PM-1 antibody is more than 1.5 times higher than that of the PM-1 antibody. The superior and unexpected property of inhibition of multiple myeloma cell growth by chimeric PM-1 antibody as compared to PM-

1 antibody illustrated in Figures 5A-C of Exhibit 1, demonstrate that the chimeric PM-1 antibody of the present invention is not obvious over Hirata or Kishimoto in view of Oi or Morrison.

Furthermore, superior inhibition of multiple myeloma cell growth by chimeric PM-1 antibody as compared to chimeric AUK12-20 is illustrated by comparing the data reported in Figure 5 (p. 854) of Exhibit 1 to the data reported in Figure 6 (p. 380) of Exhibit 2. For example, Figure 5A of Exhibit 1 and Figure 6C of Exhibit 2 show a comparison of the effect of PM-1 and AUK12-20 antibodies, respectively, on multiple myeloma cell growth using MMS1 cells. In Exhibit 1, the hollow triangles represent PM-1 antibody and the hollow circles represent chimeric PM-1 antibody. In Figure 6C of Exhibit 2, the shaded triangles represent AUK12-20 antibody and the hollow triangles represent chimeric AUK12-20 antibody. The IC_{50}'s of PM-1 antibody and AUK12-20 antibody for inhibition of multiple myeloma cell growth using MMS1 are 800 ng/ml and 800 ng/ml, respectively (see sentence bridging pp. 852-854 of Exhibit 1 and first full paragraph on the right hand side of the page on page 379 of Exhibit 2). It is clearly evident that in Figure 6 of Exhibit 2, the data for AUK12-20 antibody and chimeric AUK12-20 overlap with one another and the IC_{50}'s are nearly indistinguishable. In contrast, as discussed above, in Figure 5A of Exhibit 1, the data for PM-1 antibody and chimeric PM-1 antibody do not overlap, the IC_{50}'s are clearly distinguishable, and it is clear that the activity of the chimeric PM-1 antibody is greater than that of the PM-1 antibody. The IC_{50}'s of the PM-1 and AUK12-20 antibodies are very similar, yet the chimeric PM-1 antibody has the unexpected advantage of better inhibition of multiple myeloma cell growth while the chimeric AUK12-20 antibody does not. This unexpected result is also apparent when one compares the data reported in Figure 5B of Exhibit 1 to Figure 6B of Exhibit 2. Therefore, a person of ordinary skill in

the art could not have expected the superior properties of the chimeric PM-1 antibody. Thus, the present invention is not obvious over Hirata or Kishimoto in view of Oi or Morrison.

CONCLUSION

As the above-presented amendments and remarks address and overcome all of the rejections presented by the Examiner, withdrawal of the rejections and allowance of the claims are respectfully requested.

If the Examiner has any questions concerning this application, he or she is requested to contact the undersigned.

Respectfully submitted,

June 20, 2001
Date

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

VERSION WITH MARKINGS TO SHOW CHANGES MADE:

IN THE CLAIMS:

67. A chimeric antibody to human interleukin-6 receptor (IL-6R), comprising:

(1) light chains (L chains) each comprising a human L chain constant region (C region) and an L chain variable region (V region) of a mouse monoclonal antibody to human IL-6R; and

(2) heavy chains (H chains) each comprising a human H chain C region, and H chain V region of a mouse monoclonal antibody to human IL-6R;wherein the mouse L chain V region includes an amino acid sequence shown in SEQ ID ~~Nos: 24 or~~ NO: 28 and the mouse H chain V region includes an amino acid sequence shown in ~~SEQ ID Nos: 26 or~~ SEQ ID NO: 30.

68. The chimeric antibody according to claim 67, wherein the human L chain C region is a human Kc region.

69. The chimeric antibody according to claim 67, wherein the H chain C region is a human γ-1C region.

70. The chimeric antibody according to claim 68, wherein the H chain C region is a human γ-1C region.

71. An isolated DNA encoding an L chain comprising a human L chain C region and an L chain V region of a mouse monoclonal antibody to human IL-6R wherein the human L chain C region is a human Kc region and the L chain V region includes the amino acid sequence set forth in ~~SEQ ID NOS: 24 or~~ SEQ ID NO: 28.

72. An isolated DNA encoding an H chain comprising a human H chain C region and an H chain V region of a mouse monoclonal antibody to IL-6R, wherein the human H chain C region is a human γ-1C region and the H chain V region includes the amino acid sequence set forth in ~~SEQ ID NOS: 26 or~~ SEQ ID NO: 30.

73. An expression vector comprising a DNA coding for an L chain comprising a human L chain C region and L chain V region of a mouse monoclonal antibody to human IL-6R, wherein the human L chain C region is a human Kc region, and the L chain V region includes an amino acid sequence shown in ~~SEQ ID NOS: 24 or~~ SEQ ID NO: 28.

74. An expression vector comprising a DNA coding for an H chain comprising a human H chain C region and H chain V region of a mouse monoclonal antibody to human IL-6R, wherein the human L chain C region is a human Kc region, and the L chain V region includes an amino acid sequence shown in ~~SEQ ID NOS: 26 or~~ SEQ ID NO: 30.

75. A host cell co-transformed with:

(1) an expression vector comprising a DNA coding for an L chain comprising a human L chain C region and an L chain V region of a mouse monoclonal antibody to human IL-6R, and with

(2) an expression vector comprising a DNA coding for an H chain comprising a human H chain C region and an H chain V region of a mouse monoclonal antibody to IL-6R, wherein the human L chain C region is a human Kc region; the L chain V region includes an amino acid sequence shown in ~~SEQ ID NOS: 24 or~~ SEQ ID NO: 28, the human L chain C region is a human γ-1C region and the H chain V region includes an amino acid sequence shown in ~~SEQ ID NOS: 26 or~~ SEQ ID NO: 30.

76. A method of producing the chimeric antibody to human IL-6R according to claim 67, said method at least comprising the steps of:

(a) culturing host cells co-transformed with a first expression vector and a second expression vector, for a time and under conditions sufficient for expression to occur, wherein the first expression vector comprises DNA encoding a human L chain C region and a mouse L chain V region including the sequence set forth in ~~SEQ ID NOS: 24 or~~ SEQ ID NO: 28 and the second expression vector comprises DNA encoding a human H chain C region and a mouse H chain V region including a sequence set forth ~~in SEQ ID NOS: 26 or~~ SEQ ID NO: 30; and

(b) recovering the chimeric antibody from the culture.--

GAU 1642

Atty. Dkt. No. 053466/0234

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: **Masayuki TSUCHIYA, *et al.***

Title: **RESHAPED HUMAN ANTIBODY TO HUMAN INTERLEUKIN-6 RECEPTOR**

Appl. No.: **09/114,285**

Filing Date: **July 13, 1998**

Examiner: **G. Bansal**

Art Unit: **1642**

AMENDMENT TRANSMITTAL

Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith is Amendment A in the above-identified application.

[ ] Small Entity status under 37 C.F.R. § 1.9 and § 1.27 has been established by a Small Entity statement previously submitted.

[ ] Small Entity statement is enclosed.

[**X**] The fee required for additional claims is calculated below:

	Claims as Amended		Previously Paid For		Extra Claims Present		Rate		Additional Claims Fee
Total Claims:	10	–	20	=	0	x	$18.00	=	$0.00
Independents:	6	–	6	=	0	x	$80.00	=	$0.00
First presentation of any Multiple Dependent Claims:						+	$270.00	=	$0.00
							CLAIMS FEE TOTAL:	=	$0.00

[**X**] Applicant hereby petitions for an extension of time under 37 C.F.R. §1.136(a) for the total number of months checked below:

[ ]	Extension for response filed within the first month:	$110.00	$0.00
[ ]	Extension for response filed within the second month:	$390.00	$0.00
[X]	Extension for response filed within the third month:	$890.00	$890.00
[ ]	Extension for response filed within the fourth month:	$1,390.00	$0.00
[ ]	Extension for response filed within the fifth month:	$1,890.00	$0.00
		EXTENSION FEE TOTAL:	$890.00
		CLAIMS AND EXTENSION FEE TOTAL:	$890.00
[ ]		Small Entity Fees Apply (subtract ½ of above):	$0.00
		TOTAL FEE:	$890.00

[ ] Please charge Deposit Account No. 19-0741 in the amount of $890.00 . A duplicate copy of this transmittal is enclosed.

[**X**] A check in the amount of $890.00 is enclosed.

[**X**] The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date June 20, 2001

By Michael D. Kaminski
Reg. No. 32,904, for
Harold C. Wegner
Attorney for Applicant
Registration No. 25,258

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